Remarks

Applicants are in receipt of the Office Action mailed September 29, 2005. Applicants also gratefully acknowledge Examiner Spivack's courtesy in granting a telephonic interview in the present application. The telephonic interview was conducted on December 12, 2005, and the presently pending grounds of rejection pursuant to 35 USC 103(a) were discussed; however an agreement as to allowable claims was not reached. Applicants hereby file a Request for Continuing Prosecution (RCE), and have the following comments.

New claims 24-26 have been newly added. These claims find support in the specification at, for example, pages 9, 10 and 12-14.

REJECTIONS PURSUANT TO 35 USC §103(a)

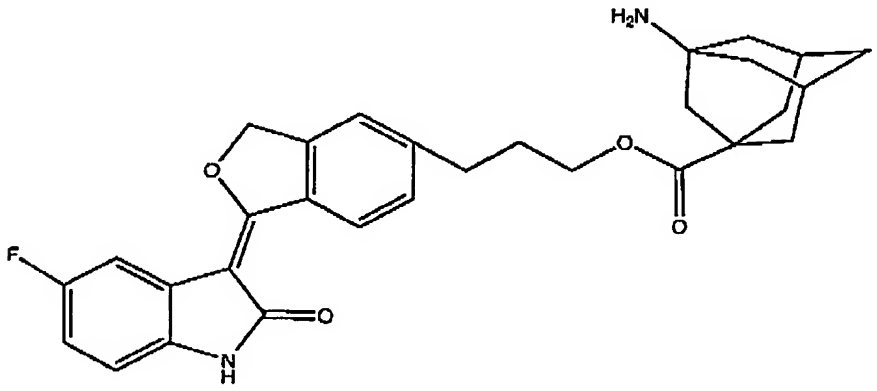
Claims 1-6,8,9,11-13, 15 and 16 remain rejected as allegedly obvious over the combination of Desantis (U.S. Patent Publication 2001/0047012) and Collins et al., (WO 01/92288). Applicants respectfully but firmly believe the claims are not obvious over these references, and offer the following arguments in support of their position. In addition, the Applicants here describe data showing that the described prodrugs are selectively targeted to melanin-containing cells in the posterior segment of the eye, as described in the specification.

The present invention comprises an ophthalmic composition comprising a conjugated molecule comprising an EEC and a TC; in

claims 8 and 24-26 the therapeutic component contains a quinoxoline component, which, in claim 26 may be brimonidine tartrate. Upon administration of the ophthalmic composition, the EEC not only increases the partition coefficient of the TC, but selectively targets the TC to the retina. See e.g., Specification, page 11, lines 3-28.

The September 29, 2005 Office Action points out that the specification uses "hypothetical" language, quoting the specification as stating that "the binding of the EECs to the retinal epithelium *may cause* the TCs to become more bioavailable. " (emphasis provided in the Office Action). Respectfully, this argument, which appears to express incredulity at the subject matter of the claims, appears more suitable to a 35 U.S.C. 101 utility rejection than the present standing rejection, which alleges obviousness pursuant to 35 U.S.C. 103(a). Nevertheless, the Applicants hereby offer experimental evidence of functionality.

The following compound, comprising an embodiment of the claimed compositions, was synthesized:



A melanin binding study was conducted using this prodrug, designated Compound A. Compound A comprises a tyrosine kinase inhibitor bound to adamantaneamine.

Concentrations of Compound A ranging from 5 μM to 40 μM were incubated with 1 mg/ml of melanin in deionized water. After 15 minutes incubation, Compound A was almost entirely bound to the melanin after 15 minutes at all tested concentrations, indicating that saturation of the melanin by the prodrug had not been reached. The data are shown in Table 1, shown below. The binding of the adamantineamine to melanin was rapid, reaching equilibrium within an incubation time of 15 minutes.

Table 1. Bound Concentrations of AGN 208483 in 1 mg/ mL Sepia Melanin

Compound A Conc. (μM)	Compound A Free (μM)	Compound A Bound (μM/mg)
4.98	1.42	3.56
9.95	1.42	8.53
19.90	1.47	18.43
29.85	1.61	28.24
59.69	1.65	58.04

Another experiment used a lower concentration of melanin in an attempt to determine saturation concentrations of Compound A, in vitro. Under similar conditions as in the previously described experiment, 0.02 mg/ml of melanin was incubated with Compound A at concentrations ranging from 10 to 40 μM. Again, the amount of Compound A bound to the melanin was a function of

the amount added to the incubation mixture at all concentrations, thus indicating that saturation had not yet occurred. The data is shown in Table 2.

Table 2. Bound Concentrations of Compound A in 0.02 mg/ mL Sepia Melanin

Compound A Conc. (μM)	Compound A Bound (μM/mg)
10.25	9.01
20.5	15.9
30.74	23.25
40.99	30.48

Therefore, these experiments show that the compounds of the present invention have the ability to quickly and selectively bind melanin, a compound found in high concentrations in the retinal pigmented epithelial (RPE) cells located in the posterior segment of the eye. Because of this selective binding capacity, this experiment thus shows that the prodrugs of the present invention have the ability to target the RPE cells of the posterior segment of the eye.

With regard to the applied prior art references, the Applicants herby incorporate by reference the remarks containing in pages 10-15 of the Reply filed July 13, 2005. Additionally, the Applicants offer the following additional reasons why the combination of Desantis and Collins does not suggest the presently claimed invention.

The present invention comprises an ophthalmic composition comprising a conjugated molecule comprising an EEC and a TC. The EEC is an adamantine defined by the structure contained in the claims; the specification indicates that EECs cause the prodrug to bind to the retinal epithelium. Thus, the produg of the present invention has the novel ability to direct the TC to the posterior segment of the eye.

Desantis discloses a combination therapy for treating glaucoma and ocular hypertension with glutamate antagonists and IOP lowering agents. Ocular hypertension is a phenomenon of the anterior segment of the eye, due to either excess secretion of aqueous humor or decreased aqueous humor outflow through the trabecular meshwork. Desantis states that the use of IOP lowering agents is intended to prevent damage to retinal ganglion cells "brought on by mechanical, circulatory and other poorly understood factors related to elevated IOP." DeSantis, ¶ [0007]. Thus, the required situs of action for the IOP lowering agents of DeSantis is the anterior segment of the eye, since it is in this locus that elevated IOP may be affected.

DeSantis therefore teaches away from applying an IOP lowering agent (such as quinoxoline derivatives including the drug brimonidine) to the posterior segment of the eye. As shown in the experiment described above, the prodrugs of the present invention bind selectively to melanin contained in the retinal epithelium of the eye.

Of course, the TCs of the present invention are not limited to IOP lowering agents. However, with respect to such agents one of ordinary skill in the art would not, based on DeSantis, be motivated to make the prodrug of the present invention, as such a prodrug would not target the IOP lowering drug to the anterior agent of the eye in accordance with DeSantis' disclosure.

The addition of Collins to DeSantis does not make up for this deficiency. Certainly Collins discloses conjugates comprising a targeting agent (the vitamin moiety) and therapeutically significant agents (antimicrobials). However, Collins does not disclose or suggest the compositions or compounds disclosed in the present specification, not does it disclose targeting the retinal epithelium of the posterior segment of the eye.

For these reasons the Applicants respectfully request the Examiner to reconsider and withdraw the rejection of the present claims under 35 U.S.C. §103(a).

Conclusion

In conclusion, Applicants have shown that the present claims are not obvious in light of the prior art of record under 35 U.S.C. §§ 103. Therefore, the pending claims are in condition for allowance, and Applicant respectfully requests the Examiner to pass the above-identified application to issuance at an early date. The Reply is being submitted in conjunction with a Request for Continuing Prosecution; should there be any deficiency associated with the filing of this communication please use Deposit Account 01-0885 for the payment of such deficiency. Should any matters remain unresolved, the Examiner is earnestly invited to call Applicant's attorney at the telephone number given below.

Respectfully submitted,

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